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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,090	12/14/1999	AXEL ULLRICH	2923-0347	3321

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EXAMINER
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LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/461,090	<b>Applicant(s)</b> ULLRICH ET AL.	
	<b>Examiner</b> Frank W Lu	<b>Art Unit</b> 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 05 May 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 39-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 39-45 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

**DETAILED ACTION**

***Continued Examination***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2005 has been entered. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on May 5, 2005. The claims pending in this application are claims 39-45.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 39-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed composition/or methods are not described in the instant disclosure, claims 39-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as containing

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subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Independent claims 39 and 45 have a limitation “G protein mediated extracellular signal transduction pathway”. Although the specification describes G protein mediated signal transduction and G-protein-coupled receptors (see specification, page 1), the specification fails to define or provide any disclosure to support such claim limitation. Furthermore, in applicant’s remarks filed on May 5, 2005, applicant does not indicate which part in the specification supports such claim limitation.

MPEP 2163.06 notes “IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.” MPEP 2163.06 further notes “WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT “NEW MATTER” IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*” (emphasis added).

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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6. Claim 44 is rejected as vague and indefinite because growth factor precursor is not a ligand of a receptor tyrosine kinase but a growth factor can be a ligand of a receptor tyrosine kinase. Please clarify.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 39, 40, and 42-45 are rejected under 35 U.S.C. 102(a) as being anticipated by Dong *et al.*, (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

Dong *et al.*, teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor.

Regarding claims 39, 40, 42, and 43, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteases and batimastat is a metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway

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and claim 39 does not require that stimulating step must be performed before contacting step, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) which acts on a growth factor precursor (by preventing EGFR ligand such as EGF release) in a G protein mediated extracellular signal pathway as recited in claim 39. Since Dong *et al.*, teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see Figure 4, column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF. Therefore, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see canceled claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) as recited in claim 39 wherein said tyrosine kinase is EGFR as recited in claims 40, 42, and 43.

Regarding claim 44, Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see canceled claim 36 of

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this instant application) and Dong *et al.*, teach that batimastat decreases level of EGFR tyrosine phosphorylation in the HMEC cells (see page 6238, right column and Figure 4), Dong *et al.*, disclose contacting a cell containing a receptor tyrosine kinase (ie., a HMEC cell) capable of activation by G-protein mediated signal transduction with a test compound (ie., batimastat) as recited in the claim. Since Dong *et al.*, teach that batimastat is a selective metalloprotease inhibitor that prevents EGFR ligand release (see page 6235, abstract and right column, and page 6239, right column, last paragraph) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.*, disclose a test compound (ie., batimastat) suspected of acting on a growth factor precursor (by preventing EGFR ligand release) which is a ligand precursor of the receptor tyrosine kinase (ie., EGFR) as recited in the claim. Since Dong *et al.*, teach to compare the level of EGFR tyrosine phosphorylation of the HMEC in the presence of batimastat, antagonist mAb225 or EGF (see Figure 4), Dong *et al.*, disclose evaluating G-protein mediated receptor tyrosine kinase (ie., EGFR) activation upon exposure of the cell (ie., the HMEC cells) to said test compound (ie., batimastat) as an indication of said test compound's ability (ie., with or without ability) to modulate G-protein mediated signal transduction thereby identifying a test compound for modulating G-protein mediated signal transduction as recited in the claim.

Regarding claim 45, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteases and batimastat is a

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metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway and claim 45 does not require that stimulating step must be performed before contacting step, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) which acts on a growth factor precursor (by preventing EGFR ligand such as EGF release) in a G protein mediated extracellular signal pathway as recited in claim 45. Since Dong *et al.*, teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see Figure 4, column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF. Therefore, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see canceled claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) wherein said tyrosine kinase is EGFR as recited in claim 45. Since it is known that EGFR has an extracellular domain and a cell comprising EGFR has a G-protein mediated signal transduction pathway wherein



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EGFR activation occurs by tyrosine phosphorylation of EGFR (see the specification, page 1, last paragraph, and page 2, second paragraph), Dong *et al.*, disclose that said receptor tyrosine kinase is EGFR and said cell (ie., the HMEC cell) comprising the extracellular domain of EGFR and having a G-protein mediated signal transduction pathway wherein one or more tyrosine residues are phosphorylated based on the activation of said G-protein mediated signal transduction pathway as recited in claim 45. Since Dong *et al.*, teach that EGF is generated from its membrane-anchored precursor by one of the ADAM family of metalloproteases (see page 6235, abstract) and it is known that EGF binds to the extracellular domain of EGFR, Dong *et al.*, disclose that the extracellular domain of said receptor (ie., EGFR) is capable of binding to its receptor ligand (ie., EGF) and said ligand is generated from a precursor of said ligand (ie., the precursor of EGF) by a proteinase-dependent cleavage (ie., one of the ADAM family of metalloproteases) thereby modulating the receptor tyrosine kinase activation by G-protein mediated signal transduction as recited in claim 45.

Therefore, Dong *et al.*, teach all limitations recited in claims 39, 40, and 42-45.

### ***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dong *et al.*, (May, 1999) as applied to claims 39, 40, and 42-45 above, and further in view of Miyoshi *et al.*, (J. Biol. Chem., 272, 14349-14355, 1997).

The teachings of Dong *et al.*, have been summarized previously, *supra*.

Dong *et al.*, do not disclose that said precursor of the ligand for the receptor tyrosine kinase is proHB-EGF as recited in claim 41.

Miyoshi *et al.*, do teach a cell line, AH66tc, that can produce proHB-EGF and contains EGFR (see abstract in page 14349, right column in page 14351, and Figure 4 in page 14352).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used AH66tc to perform the method recited in claim 39 in view of the references of Dong *et al.*, and Miyoshi *et al.*, so that HB-EGF released from pro-HB-EGF can activate EGFR by binding to its extracellular domain. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of cell line that is capable to produce a ligand of EGFR (ie., a human mammary epithelial cell line that can produce EGF taught by Dong *et al.*,) from another kind of cell line that is capable to produce a ligand of EGFR (ie., AH66tc that can produce HB-EGF taught by Miyoshi *et al.*,) during the process of performing the method recited in claim 41 would have been, in the absence

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of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the method steps of claim 41 since it is known that a variety of ligands such as HB-EGF in addition to EGF have been shown to stimulate EGFR and is released from their membrane-anchored precursors (see Dong *et al.*, page 6235, left column).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

### ***Response to Arguments***

In page 6, third paragraph bridging to page 6, second paragraph of applicant's remarks, applicant argues that "[T]he present claims include a step of 'contacting the cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway'. Dong does not disclose such a step as Dong suggests only Batimastat, which is a compound which acts on a metalloproteinase. In addition, applicants respectfully point out that the addition of EGF as disclosed in Dong, does not activate the G-protein or GPCR initiated extracellular signal transduction pathway. The addition of EGF causes a stimulation of EGFR which is different from the stimulation which proceeds via the G-protein or GPCR initiated extracellular signal transduction pathway as required in the present claims. Figure 4 in

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the present application shows the influence of the addition of various reagents such as TPA, bombesin, carbachol and EGF, on the stimulation of the GPCR-initiated signal transduction pathway. This stimulation is shown by the detection of processed HB-EGF-I (Fig 4A). Though the detection of processed HB-EGF-1 is possible after the addition of TPA, bombesin, and carbachol, no HB-EGF-I is detectable after preincubation with EGF (fig. 4a, right column). Figure 4a in the present application clearly shows that EGF, in contrast to TPA, bombesin and carbachol, is not an activator of the GPCR initiated signal transduction pathway. In view of this, applicants contend that Dong does not show stimulation of the G-protein of a GPCR-initiated extracellular signal transduction pathway or contacting the cell with a compound which acts on a growth factor precursor as required in the present claims”.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteases and batimastat is a metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), and interaction between EGFR ligand and EGFR is a key for GPCR stimulation (see the specification, page 1, last paragraph), Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) which acts on a growth factor precursor (by preventing EGFR ligand such as EGF release) in a G protein mediated extracellular signal pathway as

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recited in claim 45. Second, since interaction between EGFR ligand and EGFR is a key for GPCR stimulation (see the specification, page 1, last paragraph), the addition of EGF causes a stimulation of EGFR must play an important rule in G-protein or GPCR initiated extracellular signal transduction pathway. Thus, the applicant's statement "[T]he addition of EGF causes a stimulation of EGFR which is different from the stimulation which proceeds via the G-protein or GPCR initiated extracellular signal transduction pathway" is incorrect. Third, although, after preincubation with EGF, there is no HB-EGF-1 is detected in COS-7 cell having either M1R or BombR and VSV-proHB-EGF (see page 8 and Figure 4 a)), the claims do not require that the G protein mediated signal transduction pathway must correlate with cleavage of Pro-HB-EGF.

### *Conclusion*


11. No claim is allowed.
12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

  
**FRANK LU**  
**PATENT EXAMINER**

Frank Lu  
PSA  
July 21, 2005